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(54) Title: PROCESS FOR THE PRODUCTION OF PAROXETINE HYDROCHLORIDE

(57) Abstract: A process for the preparation of paroxetine hydrochloride in which a suspension of paroxetine maleate is treated with an excess of hydrogen chloride to form a solution containing paroxetine, maleic acid, and hydrochloric acid, and crystallising substantially pure paroxetine hydrochloride from the solution. In this process paroxetine maleate in solution is directly converted to solid paroxetine hydrochloride, avoiding formation of paroxetine free base and subsequent re-acidifying with hydrogen chloride. The process surprisingly results in good yield and purity without the complication of large amounts of maleic acid contamination, and so is suitable for large-scale manufacture.

PROCESS FOR THE PRODUCTION OF PAROXETINE HYDROCHLORIDE

This invention is concerned with a process for conversion of paroxetine maleate to paroxetine hydrochloride, more specifically for the direct conversion of paroxetine maleate to paroxetine hydrochloride.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-) *trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylenedioxy-phenoxymethyl)-piperidine. This compound is used in therapy as the hydrochloride salt for the treatment and prophylaxis of *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

Example 2 of US 4,007,196 describes the preparation of a paroxetine maleate salt. Paroxetine free base is dissolved in ether and treated with a solution of maleic acid in ethyl ether to form a crystalline product, which is recrystallised from 99% ethanol-ether to give a maleate salt melting 136-8°C. Apart from the melting point, there is no characterizing data that allows an unambiguous assignment of structure. PCT/GB99/01106 describes the preparation of paroxetine maleate 1:1 and 2:1 salts and polymorphs.

Paroxetine may be isolated and stored in the form of its maleate salt, but for medicinal use the hydrochloride form is preferred, either as the crystalline hemihydrate (as disclosed in EP-A-0223403) or as one of the anhydrate forms (e.g. as disclosed in WO 96/24595).

Example 2 of EP-A-0 223 403 describes the conversion of paroxetine acetate to paroxetine hydrochloride by acidification of an aqueous solution of paroxetine acetate with concentrated hydrochloric acid and crystallisation therefrom. Further, Example 8 of EP-A-0 223 403 describes the conversion of a solution of paroxetine acetate in propan-2-ol to paroxetine hydrochloride by treatment with a solution of concentrated hydrochloric acid in propan-2-ol at 0°C for 16 hours.

We have found that pure solid paroxetine hydrochloride is not obtained when the procedures of Examples 2 and 8 of EP-A-0 223 403 are applied to paroxetine maleate. Furthermore, acetic acid is volatile and easily removed during drying, unlike maleic acid, which has to be removed completely during crystallisation otherwise residues will contaminate the product.

This invention is based on the discovery of a procedure by which paroxetine maleate in suspension is directly converted to solid paroxetine hydrochloride, avoiding formation of paroxetine free base and subsequent re-acidifying with hydrogen chloride. The process surprisingly results in good yield and purity without the complication of large amounts of maleic acid contamination, and so is suitable for large-scale manufacture.

The solubility of paroxetine maleate in propan-2-ol is less than 0.5% by weight, so reactions based on paroxetine maleate in solution would be very volume inefficient and unsuitable for manufacture. Conversion of one solid into another in a slurry is likely to result in incomplete conversion and an impure product. Indeed we have found that if one equivalent of hydrogen chloride is used a mixed product is obtained.

Surprisingly we have found that if an excess of hydrogen chloride is used, a stable mixed maleate/hydrochloride solution from which can be isolated solid crystalline paroxetine hydrochloride free of contamination with maleic acid.

Accordingly, this invention provides a process for the preparation of paroxetine hydrochloride in which a suspension of paroxetine maleate is treated with an excess of hydrogen chloride to form a solution containing paroxetine, maleic acid, and hydrochloric acid, and crystallising substantially pure paroxetine hydrochloride from the solution.

The hydrogen chloride may be added as an aqueous or non-aqueous solution or in the form of a gas or as an amine hydrochloride salt (for example ammonium chloride or triethylammonium chloride) as a solid or in solution. Preferably the hydrogen chloride solution is added slowly. Preferably the excess of hydrogen chloride is in the range 5-100%, more preferably it is in the range 7-15% (on a molar basis).

The conversion reaction may be carried out at any temperature between 0°C and 80°C, but most conveniently it is carried out at about 15-25°C.

Optionally the solution may be filtered or clarified.

One surprising feature of the invention is that the product that crystallises from the mixed solution is in fact the more soluble salt.

Preferably crystallisation is initiated by seeding with crystals of the desired final form of paroxetine hydrochloride, such as the hemihydrate, or the anhydrate Form A, B, or C.

Suitable solvents for the conversion are those from which paroxetine hydrochloride is known to crystallise, for example alcohols, such as propan-2-ol, and ketones, such as butanone, optionally mixed with water, or a hydrocarbon, such as toluene. Suitable volumes of solvent are in the range 5-30 volumes (based on the weight of paroxetine maleate), preferably in the range 10-20 volumes.

In certain solvents, for example propan-2-ol, paroxetine hydrochloride will crystallise as a solvate. In such cases the solvent may be removed from the solvate by known methods

Paroxetine maleate salts used in this invention may be prepared as disclosed in US 4007196 or PCT/GB99/01106.

Paroxetine hydrochloride obtainable by the process of this invention may be used to treat and prevent the following disorders:

Alcoholism	Anxiety
Depression	Obsessive Compulsive Disorder
Panic Disorder	Chronic Pain
Obesity	Senile Dementia
Migraine	Bulimia
Anorexia	Social Phobia
Pre-Menstrual Syndrome (PMS)	Adolescent Depression
Trichotillomania	Dysthymia
Substance Abuse	

These disorders are herein after referred to as "the Disorders".

The present invention further provides a method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of paroxetine hydrochloride obtainable by the process of this invention to a sufferer in need thereof.

The present invention further provides a pharmaceutical composition for use in the treatment and/or prevention of the Disorders which comprises an admixture of paroxetine hydrochloride obtainable by the process of this invention with a pharmaceutically acceptable carrier.

The present invention also provides the use of paroxetine hydrochloride obtainable by the process of this invention for treating and/or preventing the Disorders.

The present invention also provides the use of paroxetine hydrochloride obtainable by the process of this invention in the manufacture of a medicament for treating and/or preventing the Disorders.

Most suitably the present invention is applied to the treatment of depression, OCD and panic.

Compositions containing the salt of this invention may be formulated for administration by any route, and examples are oral, sub-lingual, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may, if desired, be designed to give slow release of the paroxetine salt.

The medicaments may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The composition is usually presented as a unit dose composition containing from 1 to 200mg of active ingredient calculated on a free base basis, more usually from 5 to

100mg, for example 10 to 50mg such as 10, 12.5, 15, 20, 25, 30 or 40mg by a human patient. Most preferably unit doses contain 20mg of active ingredient calculated on a free base basis. Such a composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 5 to 400mg of active ingredient calculated on a free base basis. Most preferably the unit dose is taken once a day.

Preferred unit dosage forms include tablets or capsules.

The compositions of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing.

Suitable carriers for use in this invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or preservative. These agents may be utilized in conventional manner, for example in a manner similar to that already used for marketed anti-depressant agents.

Specific examples of pharmaceutical compositions include those described EP-B-0-223403, and US 4,007,196 in which the products of the present invention may be used as the active ingredients.

The following Examples illustrate the invention.

Reference Example 1

Preparation of Paroxetine (1:1) Maleate Form A

Maleic acid [14.8g, 0.128 mol] was stirred in ethyl acetate [100ml] and the solution warmed gently. Paroxetine free base [42.7g] in ethyl acetate was then added rapidly with stirring and the suspension briefly became clear then immediately solidified. Warming was continued until the solution was at reflux and the mixture was then stirrable. The reaction mixture was allowed to cool with stirring and the cold solution filtered and washed with ethyl acetate [25ml] and dried in a vacuum oven at 40 °C for 3

hours to give paroxetine maleate Form A. NMR showed a ratio of 1:1 for paroxetine : maleic acid.

m.pt. 139-141°C

Reference Example 2

Paroxetine (1:1) Maleate Form B by recrystallization of Form A from butanone.

A suspension of paroxetine maleate Form A (0.5g) in butanone (4 ml) was stirred vigorously and heated to reflux. The solution was allowed to cool slowly to room temperature to give a paroxetine maleate Form B as a granular white crystalline solid which was collected by filtration and dried in vacuo over phosphorous pentoxide. NMR showed a ratio of 1:1 for paroxetine : maleic acid; butanone content was approximately 0.1% by weight.

m.pt. 136-138°C

Example 1

Paroxetine (1:1) maleate Form A (5.67 g) in propan-2-ol (50 ml) was stirred rapidly and treated with a solution of hydrogen chloride in propan-2-ol (2.5 ml of a ca. 5.5 molar solution) over 15 minutes. A solution formed, and was stirred for 30 minutes at room temperature before seeds of paroxetine hydrochloride anhydrate Form A (0.1 g) were added. Crystallisation commenced rapidly giving a thick suspension which was mobilized by the addition of more propan-2-ol (50 ml). The product, paroxetine hydrochloride propan-2-ol solvate was collected by filtration, washed with propan-2-ol (30 ml), and dried under vacuum at 60°C for 5 hours. Yield 2.73 g, propan-2-ol content 11% by weight.

Example 2

Paroxetine maleate Form A (5.00 g) in propan-2-ol (50 ml) was stirred rapidly and treated with a solution of hydrogen chloride in propan-2-ol (2.8 ml of a ca. 5.5 molar

solution) over 10 minutes. Insoluble residues were removed by filtration and the resulting clear solution was stirred for 30 minutes at room temperature. Seeds of paroxetine hydrochloride anhydrate Form A were added (0.1 g), causing rapid crystallisation to a thick suspension that was mobilised by adding more propan-2-ol (50 ml). The product, paroxetine hydrochloride propan-2-ol solvate was collected by filtration, washed with propan-2-ol (50 ml), and dried under vacuum at 60°C for 5 hours. Yield 3.07 g, propan-2-ol content 6% by weight.

Example 3

Paroxetine maleate Form A (2.00 g) in methyl 2-pentanone (20 ml) was stirred rapidly and treated with a solution of hydrogen chloride in propan-2-ol under nitrogen (1.35 ml of a ca. 5.5 molar solution). The solid reagents dissolved and the solution was stirred for 30 minutes at room temperature. Seeds of paroxetine hydrochloride anhydrate Form C were added and the reaction mixture was insonicated. Crystallisation occurred and the mixture was stirred at room temperature for 3 hours. The product, paroxetine hydrochloride anhydrate Form C, was collected by filtration, washed with methyl 2-pentanone, and dried under vacuum at 60°C overnight (yield 1.32 g).

Example 4

A stirred suspension of paroxetine maleate Form B (2.00 g) in propan-2-ol (20 ml) was treated with 1M hydrochloric acid (10 ml). A homogoneous solution resulted, and was seeded with paroxetine hydrochloride hemihydrate, cooled and concentrated to 75% the original volume by evaporation at reduced pressure. The crystallising mixture was stirred for 1 hour. After filtering, washing with water, and drying under vacuum at 60°C, the product was found to be paroxetine hydrochloride hemihydrate, free of maleic acid contamination. Yield 0.86 g.

Example 5

A suspension of paroxetine maleate Form B (2.00 g) in propan-2-ol (50 ml) was stirred rapidly at ambient temperature and treated with 5 molar hydrochloric acid (1.0 ml). The mixture was stirred for 3 hours, filtered, washed with propan-2-ol, and dried under vacuum to give crystalline paroxetine hydrochloride hemihydrate. Yield 1.36 g.

CLAIMS

1. A process for the preparation of paroxetine hydrochloride in which a suspension of paroxetine maleate is treated with an excess of hydrogen chloride to form a solution containing paroxetine, maleic acid, and hydrochloric acid, and crystallising substantially pure paroxetine hydrochloride from the solution.

2. A process according to claim 1, in which hydrogen chloride is added as an aqueous or non-aqueous solution or in the form of a gas or as an amine hydrochloride salt as a solid or in solution.

3. A process according to claim 1 or 2, in which the excess of hydrogen chloride is in the range 5-100% (on a molar basis).

4. A process according to any preceding claim, in which the conversion is carried out at a temperature between 0°C and 80°C, but most conveniently it is carried out at about 15-25°C.

5. A process according to any preceding claim, in which crystallisation is initiated by seeding with crystals of paroxetine hydrochloride hemihydrate, or the anhydrate Form A, B, or C.

6. A process according to any preceding claim, in which paroxetine hydrochloride crystallises as a solvate, and the solvent is removed from the solvate.

7. A method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of paroxetine hydrochloride obtainable by a process according to any one of claims 1 to 6 to a sufferer in need thereof.

INTERNATIONAL SEARCH REPORT

Internat ıl Application No
PCT/GB 00/02425

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 56787 A (SYNTHON B V) 17 December 1998 (1998-12-17) * see proceeees on pages 6/7 * the whole document ---	1-7
Y	WO 96 24595 A (SMITHKLINE BEECHAM PLC ;JACEWICZ VICTOR WITOLD (GB); WARD NEAL (GB) 15 August 1996 (1996-08-15) cited in the application the whole document ---	1-7
Y	BUXTON P C ET AL: "SOLID-STATE FORMS OF PAROXETINE HYDROCHLORIDE" INTERNATIONAL JOURNAL OF PHARMACEUTICS,NL,AMSTERDAM, vol. 42, 1988, pages 135-143, XP000572028 ISSN: 0378-5173 the whole document --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
23 October 2000	30/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stellmach, J

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INTERNATIONAL SEARCH REPORT

Internal Application No.
PCT/GB 00/02425

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 223 403 A (BEECHAM GROUP PLC) 27 May 1987 (1987-05-27) cited in the application the whole document	1-7
P,X	WO 99 52901 A (MAN JOHN ;JACEWICZ VICTOR WITOLD (GB); JONES ALAN DAVID (GB); SMIT) 21 October 1999 (1999-10-21) the whole document	1-7

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INTERNATIONAL SEARCH REPORT

mation on patent family members

Interna[illegible]l Application No
PCT/GB 00/02425

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9856787 A	17-12-1998	US 5874447 A	23-02-1999
		AU 3108097 A	30-12-1998
		BG 103980 A	31-07-2000
		BR 9714787 A	18-07-2000
		EP 0994872 A	26-04-2000
		NO 995455 A	09-02-2000
		PL 336895 A	17-07-2000
WO 9624595 A	15-08-1996	AT 21096 A	15-08-2000
		AU 701518 B	28-01-1999
		AU 4332896 A	15-08-1996
		AU 4786496 A	27-08-1996
		AU 9821398 A	04-03-1999
		BE 1009112 A	05-11-1996
		BG 100333 A	30-08-1996
		BR 9600534 A	13-05-1997
		CA 2168829 A,C	07-08-1996
		CA 2210022 A	07-08-1996
		CA 2210023 A,C	07-08-1996
		CA 2211521 A	07-08-1996
		CA 2211522 A	07-08-1996
		CH 688353 A	15-08-1997
		CH 689229 A	31-12-1998
		CH 689804 A	30-11-1999
		CN 1143643 A	26-02-1997
		CY 2015 A	20-02-1998
		CZ 9600320 A	14-08-1996
		DE 19603797 A	14-08-1996
		DE 29623383 U	20-05-1998
		DK 11996 A	07-08-1996
		EP 0808314 A	26-11-1997
		ES 2114471 A	16-05-1998
		FI 960519 A	07-08-1996
		FR 2730232 A	09-08-1996
		GB 2297550 A,B	07-08-1996
		GR 1002466 B	06-11-1996
		HK 59397 A	16-05-1997
		HU 9600255 A	28-03-1997
		IE 960104 A	07-08-1996
		IT MI960203 A	05-08-1997
		JP 2915338 B	05-07-1999
		JP 8245620 A	24-09-1996
		JP 11228571 A	24-08-1999
		LT 96007 A,B	25-10-1996
		LU 88711 A	23-08-1996
		LV 11618 A	20-12-1996
		LV 11618 B	20-04-1997
		MC 2411 A	02-12-1996
		NL 1002248 C	11-09-1996
		NL 1002248 A	06-08-1996
		NO 960472 A	07-08-1996
		NZ 280943 A	29-01-1997
		PL 312646 A	19-08-1996
		PT 101827 A,B	30-09-1996
		RO 112426 A	30-09-1997
		RU 2125052 C	20-01-1999
EP 0223403 A	27-05-1987	AU 593295 B	08-02-1990

INTERNATIONAL SEARCH REPORT

rmation on patent family members

Interna ıl Application No
PCT/GB 00/02425

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0223403 A		AU 6433286 A	30-04-1987
		BG 61323 B	30-05-1997
		CA 1287060 A	30-07-1991
		CZ 9103910 A	19-01-1994
		CY 1743 A	17-02-1995
		DE 3688827 A	09-09-1993
		DE 3688827 T	31-03-1994
		DK 61091 A	05-04-1991
		DK 508786 A	26-04-1987
		ES 2058061 T	01-11-1994
		FI 864320 A,B,	26-04-1987
		HK 125993 A	19-11-1993
		IE 59901 B	20-04-1994
		JP 1918281 C	07-04-1995
		JP 6047587 B	22-06-1994
		JP 62129280 A	11-06-1987
		NO 864237 A,B,	27-04-1987
		NZ 218047 A	29-03-1989
		PT 83608 A,B	01-11-1986
		US 4721723 A	26-01-1988
		ZA 8608064 A	30-09-1987
WO 9952901 A	21-10-1999	AU 3433499 A	01-11-1999